Original Research Article

Lactate dehydrogenase as surrogate marker of preeclampsia and eclampsia

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ABSTRACT

Background: Hypertensive disorders of pregnancy is a spectrum of disorder which include chronic hypertension that antedates pregnancy and gestational hypertension or pre-eclampsia that is unique to human pregnancy. It is still a poorly understood condition. The clinical course is progressive and characterized by continuous deterioration that is arrested only by termination of pregnancy. Hence the disease must be detected in early stage and managed appropriately for improved maternal and fetal outcome.
Methods: The study consists of 173 antenatal patients of gestational age 28 weeks and above. Study population was divided into two groups, Group 1 consists of 50 antenatal women of normotensive nature served as controls and group 2 consists of 123 antenatal women with confirmed hypertension. Venous blood samples were collected used for the estimation of lactate dehydrogenase enzyme.
Results: Out of the total 173 patients 104 women delivered by C-section, 67 by normal vaginal delivery and 2 by assisted breech delivery. Among the women who delivered by caesarean 60 (57.69%) had serum LDH less than 600, 18 (17.30%) had serum LDH between 600 and 800 and 26 (25.00%) had LDH above 800. Among the women who delivered vaginally 61 (91.04%) had LDH less than 600, 1 (1.49%) had LDH between 600 and 800 and 5 (7.46%) had LDH above 800. Only 2 women delivered by assisted breech delivery one with LDH between 600 and 800 and another with S. LDH above 800.
Conclusions: The study was done in search of a valuable marker for preeclampsia and Eclampsia which would reflect the severity of the disease and would predict the maternal and fetal outcome. Such markers can help in decision making and can influence the current management protocols in order to achieve a better maternal and perinatal outcome.

Keywords: Antenatal women, Eclampsia, Hypertension, Maternal outcome, Serum lactate dehydrogenase

INTRODUCTION

Hypertensive disorders of pregnancy are the most common medical disorders complicating pregnancy.[1] The incidence is continuously increasing due to unknown reasons and the overall incidence is 7 to 10% worldwide. One in every 100 to every 2000 pregnancy is complicated by eclampsia.[2,3] Pre-eclampsia and eclampsia as a cause of maternal mortality and morbidity is increasing worldwide both in developing and developed nations currently the contribution being 15 to 20%.[4-6]

A hypertensive disorder of pregnancy is a spectrum of disorder which includes chronic hypertension that antedates pregnancy and gestational hypertension or pre-eclampsia that is unique to human pregnancy.[7-9] It is still

a poorly understood condition. The clinical course is progressive and characterized by continuous deterioration that is arrested only by termination of pregnancy.[10-12] Hence the disease must be detected in early stage and managed appropriately for improved maternal and fetal outcome.[13]

Biochemical markers will enable prompt detection of high risk pregnancies and those who will develop clinically significant disease and hence the maternal and fetal outcome can be improved by enhancing the antenatal care to those target women.[14,15] Lactate dehydrogenase (LDH) is an intracellular enzyme which converts lactate to pyruvate and its elevated level indicates cellular death and leakage of enzyme from the cell. Increased levels of serum LDH is a marker of increased cellular death and is found in association with pre-eclampsia and eclampsia.[16-18]

Estimation of serum LDH is a simple, minimally invasive and cheap biochemical test which though nonspecific is found to be highly sensitive and a reliable parameter in estimating the severity of the disease in some studies.[19,20]

This study aims at quantitating the extent of cellular death in terms of serum LDH in patients with clinical profile of pre-eclampsia and eclampsia and thereby using serum LDH as a marker of severity of the disease.

METHODS

This is an observational study. The study consists of 173 antenatal patients of gestational age 28 weeks and above attending antenatal OPD/labour ward in Chengalpattu Medical College Hospital, Chengalpattu of Tamil Nadu during the period of November 2013 - August 2014. A total of 173 antenatal women were recruited from Outpatient department/labour ward at Chengalpattu Medical College and Hospital from November 2013 - August 2014.

All patients were of gestational age 28 weeks and above. Patients were selected based on the inclusion and exclusion criteria irrespective of the age and parity and they were divided into three groups based on NHBPEP classification as 50 mild pre-eclamptic, 50 severe pre-eclamptic and 23 eclamptic. Patients were also divided into three groups based on their serum LDH (less than 600, 600 to 800, and more than 800 IU/l). All the diagnostic components and the possible maternal and fetal complications of pre-eclampsia were correlated with their serum LDH levels.

Patients were selected based on the inclusion and exclusion criteria irrespective of the age and parity and they were divided into three groups based on NHBPEP classification as normotensives, mild pre-eclamptic, severe pre-eclamptic and eclamptic. (Mild pre-eclampsia - BP of 140/90 to <160/110 mmHg; severe pre-eclampsia

- BP ≥160/110 mmHg; eclampsia - one or more episode of GTCS).

Inclusion criteria

- Antenatal women with normal blood pressure, with hypertension falling under pre-eclampsia and eclampsia were included in the study.

Exclusion criteria

- Antenatal women with hypertension less than 20 weeks of gestation, pre-existing diabetes mellitus, renal diseases, liver disorders, thyroid disorders, epilepsy, heart disease, muscular dystrophy, leukemia, pernicious anemia, hemolytic anemia and other causes of increased LDH, HIV reactive women, meningitis were excluded from the study.

Total 2 ml of venous blood sample was collected and then centrifuged for serum separation. Serum LDH estimation was done by International Federation of Clinical Chemistry (IFCC) method using coral clinical system, commercial kit available for semi autoanalyzer's. Urine protein was estimated by urine testing strip.

Statistical analysis

Data was represented as mean and standard deviation. One-way analysis of variance (ANOVA) and the chi-square test were used to compare the results. Differences were considered significant when p <0.05.

RESULTS

Study includes total 173 antenatal women were of gestational age 28 weeks and above. Study population was divided into two groups - Group 1 is controls consists of 50 normotensive patients and Group 2 is cases further subdivided into three groups based on NHBPEP classification as 50 mild pre-eclamptic, 50 severe pre-eclamptic and 23 eclamptic. Patients were also divided into three groups based on their serum LDH levels (less than 600, 600 to 800, and more than 800 IU/L). Influence of age and parity on serum LDH were analysed using appropriate statistical test. Correlation between serum LDH and maternal and fetal complications were studied using appropriate statistical test. The following observations were made from the results derived in this study.

Distribution of age between the groups were analysed using ANOVA test. The mean age of patients in controls, mild pre-eclampsia, severe pre-eclampsia and eclampsia are 23.64, 24.46, 24.08 and 23.95 and their standard deviations are 3.08, 3.69, 3.41 and 3.92 respectively. F value is 0.47; p value is 0.70. Hence, there is no statistically significant difference in the distribution of age between groups (Table 1). Out of the total 173 women 121 patients had serum LDH levels less than 600

IU/L, 20 had values between 600 to 800 IU/L and 32 had values more than 800 IU/L. The Mean age of the patients with serum LDH less than 600, 600 to 800 and more than 800 are 23.95, 24.10 and 24.34 and their standard deviations are 3.48, 2.75 and 3.82 respectively. 2-tailed test was applied and p value is 0.21. Hence, there is no statistically significant correlation between age and serum LDH (Table 1).

Table 1: Comparison of age, blood pressure and serum LDH levels among the different study groups.

Parameters	Group 1 (n=50) (controls)	Group 2 (n=50) (mild preeclampsia)	Group 2 (n=50) (severe preeclampsia)	Group 3 (n=23) (eclampsia)
Age (years)	23.64±3.08	24.46±3.69*^	24.08±3.41**^	23.95±3.92***^
Systolic BP (mmHg)	100±10$	146±5*$	159±7**$	175±12***$
Diastolic BP (mmHg)	79±8	89±11*$	100±8**$	109±10***$
Serum LDH (IU/L)	275.40±108	381.42±109*$	660.84±104**$	1360.43±340***$

*Comparison between Group 1 and Group 2 (mild preeclampsia); ** Comparison between Group 1 and Group 2 (severe preeclampsia); ***Comparison between Group 1 and Group 2 (eclampsia). ^p value is insignificant; $p value is < 0.001 and statistically significant.

Table 2: Correlation of proteinuria with serum LDH levels among the studied population.

Urine Albumin	Serum LDH			
	<600	600-800	>800	Total
1+	3	0	0	3
2+	56	10	3	69
3+	14	6	11	31
4+	1	4	18	23

Table 3: Correlation of serum LDH levels with the mode of delivery.

Mode of delivery	Serum LDH levels in IU/L		
	<600	600-800	>800
	n (%)	N (%)	n (%)
LSCS	60 (49.59%)	18 (90.0%)	26 (81.25%)
LN	61 (50.41%)	1 (5.0%)	5 (15.63%)
Asst. breech	0 (0.00%)	1 (5.0%)	1 (3.13%)

LSCS: Low segment caesarean section, LN: Labour natural.

Serum LDH values compared among the groups using ANOVA test TUKEY HSD test was applied to study the difference in serum LDH between groups. The mean serum LDH value of controls, mild pre-eclampsia, severe pre-eclampsia and eclampsia are 275.4, 381.42, 660.84 and 1360.43 and their standard deviations are 108, 109, 104 and 340 respectively. There is no statistically significant difference in the serum LDH levels between controls and mild pre-eclampsia with p value is <0.001 but as the severity of the disease goes up there is a significant increase in serum LDH as shown in the above Table. (p <0.001; Table 1).

Out of total 121 patients with LDH levels <600 IU/l, 50 (41.32%) cases had normal SBP, 47 (38.84%) had SBP in the range of 140 to 159 mmHg and 24 (19.83%) had SBP 160 and above. Out of 20 patients with LDH levels between 600 and 800 IU/l, none had normal SBP, 12 (60%) had SBP in the range of 140 to 159 mmHg and 8 (40%) had SBP 160 and above. In the remaining 32 patients with LDH levels above 800 IU/l, none had

normal SBP, 7 (21.87%) had SBP in the range of 140 to 159 mmHg and 25 (78.12%) had SBP 160 and above (Table 1). Chi-square test was applied to study the correlation between SBP and S. LDH. Correlation coefficient is 0.369, chi-square value is 52.67 and p value is 0.001. There was a significant rise in serum LDH with systolic blood pressure (Table 1).

Out of total 121 patients with LDH levels <600 IU/l, 56 (46.28%) had normal DBP, 51 (42.14%) had DBP in the range of 90 to 109 mmHg and 14 (11.57%) had DBP 110 and above. Out of 20 patients with LDH levels between 600 and 800 IU/l, one (5%) had normal DBP, 10 (55%) had DBP in the range of 90 to 109 mmHg and 9 (45%) had DBP 110 and above. In the remaining 32 patients with LDH levels above 800 IU/l, none had normal DBP, 5 (15.6%) had DBP in the range of 90 to109 mmHg and 27 (84.37%) had DBP 110 and above. Chi-square test was applied to study the correlation between DBP and serum LDH. Correlation coefficient is 0.393, chi-square value is 75.75 and p value is 0.0001; There was a

significant rise in serum LDH with diastolic blood pressure (Table 1).

Out of the total 173 patients 41 did not have proteinuria, 6 had proteinuria in the range of 0.1 g/L and 3 had proteinuria in the range of 0.3 g/L, whose LDH levels were <600. 69 patients had proteinuria in the range of 1.0 g/L, out of which 56 (81.16%) had LDH levels <600, 10 (14.49%) had LDH levels between 600 and 800 and 3 (4.35%) had LDH levels more than 800. 31 patients had proteinuria in the range of 3.0g/L, out of which 14 (45.16%) had LDH levels <600, 6 (19.35%) had LDH levels between 600 and 800 and 11 (35.48%) had LDH levels more than 800. 23 patients had proteinuria in the range of 10.0 g/L, out of which 1 (4.35%) had LDH levels <600, 4 (17.39%) had LDH levels between 600 and 800 and 18 (78.26%) had LDH levels more than 800 (Table 2). Chi-square test was applied to study the correlation between S. LDH and severity of proteinuria. Correlation coefficient is 0.567, chi-square value is 58.35 and p value is 0.001; There was a significant rise in S. LDH with increasing proteinuria (Table 2).

Out of the total 173 patients 104 women delivered by LSCS, 67 by normal vaginal delivery and 2 by assisted breech delivery and none by instrumental delivery. Among the women who delivered by caesarean 60 (57.69%) had serum LDH less than 600, 18 (17.30%) had serum LDH between 600 and 800 and 26 (25.00%) had serum LDH above 800. Among the women who delivered vaginally 61 (91.04%) had serum LDH less than 600, 1 (1.49%) had serum LDH between 600 and 800 and 5 (7.46%) had serum LDH above 800. Only 2 women delivered by assisted breech delivery one with serum LDH between 600 and 800 and another with serum LDH above 800 IU/L (Table 3).

The incidence of operative delivery significantly increased with serum LDH levels up to 800 and then it declined probably because of the early onset of spontaneous labour in eclamptic women. When the parameters were taken as serum LDH levels less than 600 and more than 600 there was as significant increase in the incidence of operative delivery. Correlation coefficient value is 0.207, p value is 0.001. There was a significant rise in serum LDH in patients with operative delivery correlation between serum LDH and operative delivery explains the severity of the disease with increased serum LDH and the need for immediate delivery in them (Table 3).

The mean gestational age at the time of delivery in patients with serum LDH less than 600, 600 to 800 and more than 800 are 38.19, 37.05 and 34.46 and their standard deviations are 2.16, 2.89 and 3.45 respectively. Correlation coefficient is -0.276, p value is 0.001. There is reduction in the mean GA with higher level of LDH (p=0.00). This fact could be explained by the increased preterm deliveries associated with pre-eclampsia (Table 3).

DISCUSSION

This study is conducted in the department of obstetrics and gynecology, Chengalpattu Medical College. A total of 173 antenatal women were recruited from Outpatient department/labour ward at Chengalpattu Medical College and Hospital from November 2013 - August 2014. All patients were of gestational age 28 weeks and above. Patients were selected based on the inclusion and exclusion criteria irrespective of the age and parity and they were divided into three groups based on NHBPEP classification as 50 mild pre-eclamptic, 50 severe pre-eclamptic and 23 eclamptic. Patients were also divided into three groups based on their serum LDH (less than 600, 600 to 800, and more than 800 IU/l). All the diagnostic components and the possible maternal and fetal complications of pre-eclampsia were correlated with their serum LDH levels. The distribution of age and mean age between groups were almost similar. No significant difference was observed in terms of age and parity between groups and moreover they did not influence serum LDH in contrast to Qublan et al and Jaiswar et al.[5] Qublan et al stated that the mean age of patients in preeclampsia was significantly less compared to the normotensives and majority were young primigravida in the affected population.[5]

Serum LDH levels consistently increased with increasing systolic and diastolic blood pressure, more so with diastolic blood pressure with a p value of <0.001 similar to Jaiswar and Amrit et al, Jaiswar and Amrit et al in their study observed a mean serum LDH of 278.33±119.25 in normotensives, 400.45±14.21 in mild pre-eclampsia, 646.95±49.64 in severe pre-eclampsia, 1648.10±1992.29 in eclampsia with a p value <0.001. Similar results were observed in this study with mean serum LDH of 275.4±108.38 in normotensives, 381.42±178.93 in mild pre-eclampsia, 660.84±456.08 in severe pre-eclampsia and 1648±677.13 in eclampsia with a p value of <0.001.

Most of the women with severe preeclampsia and eclampsia had severe proteinuria and serum LDH significantly increased with the severity of proteinuria (p <0.00). Results were comparable to Qublan et al who showed a significant increase in serum LDH with severity of proteinuria (p value of <0.05). In a study only 2 cases had abruptio placenta but the incidence was tremendously high with 32 cases in this group. Significantly high LDH values were observed than controls p (0.00) among them.[21] Other maternal complications like CVA, Postpartum hemorrhage, renal failure were not present in the study population. Still births were not present in the study population probably because of the close fetal surveillance, early decision and increased operative delivery among pre-eclamptic women.[22-24]

The incidence of operative delivery moderately elevated with increased LDH levels and this explains the severity of the disease with increased LDH and the need for immediate delivery in them.[25] The mean gestational age

at the time of delivery in patients with serum LDH less than 600, 600 to 800 and more than 800 are 38.19, 37.05 and 34.46 and their standard deviations are 2.16, 2.89 and 3.45 respectively. The mean baby weight in patients with serum LDH less than 600, 600 to 800 and more than 800 are 2.76, 2.37 and 1.83 kg and their standard deviations are 0.54, 0.59 and 0.59 kg respectively. Mean gestational age and mean baby weight had negative correlation with serum LDH levels with p value <0.001 similar to other studies at the time of delivery was significantly less in patients with increasing LDH levels. This fact could be explained by the increased preterm deliveries and the need for early termination of pregnancy to improve the maternal outcome in view of severity of disease.[26]

Complications like growth restriction and late intrauterine fetal demise are well known complication of pre-eclampsia.[22,24-25] In some studies the serum LDH levels in pre-eclamptic women with small for gestational age infants and found a significant correlation between both. Incidence of IUGR and IUD were significantly higher in pre-eclamptic women and their serum LDH levels compared to the controls were abnormally high (p value <0.00) similar to the studies mentioned.[27,28]

CONCLUSION

After analysing the data and comparing the results following conclusion have been drawn from the study. Serum LDH values were significantly high in pre-eclamptic patients depending on the severity of the disease indicating the increased cellular turnover in them. Serum LDH levels had a good correlation with all the diagnostic components of preeclampsia like SBP, DBP and proteinuria. Hence diagnostic and management strategies may be considered based on serum LDH levels and further studies on a larger sample can be done to substantiate study observations on the utility of this parameter as a diagnostic and prognostic component of preeclampsia. Development of new management strategies based on serum LDH levels may help in appropriate decision making thereby avoiding unwanted maternal and fetal deaths.

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